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EXAMINER	
BRUMBACK, BRENDA G	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/29/2002 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/734,002	SEIKI ET AL.	
	Examiner	Art Unit	
	Brenda G. Brumback	1642	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-26 and 30-35* is/are pending in the application.

4a) Of the above claim(s) *23-25 and 30-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-22 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/000,041* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 14-22 and 26 in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 14-26 and 30-35 are pending. Claims 23-25 and 30-35 are withdrawn from consideration as directed to a nonelected invention. Claims 14-22 and 26 are under examination on the merits.

Information Disclosure Statement

The Information Disclosure Statement filed 12/12/2000 has been considered. A signed copy is attached hereto.

Claim Rejections - 35 USC § 112

Claims 14-22 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite for reciting the abbreviations "MMPs", "MT-MMP", and "pro MMP-2" without disclosing the full the name of the proteins for which the abbreviations stand. It is suggested that at the first occurrence of each of the abbreviations, the claims be amended to recite the full name of the protein followed by the abbreviation in parentheses, *i.e.*, matrix metalloproteinases (MMPs).

The claims are also indefinite for recitation of the terms "MT-MMP-1","MT-MMP-2", "pro MMP-2", and "MT-MMP-3", as it is not clear what specific proteins are encompassed within the claimed invention. While the specification discloses that MT-MMP-1 and MT-MMP-2 are capable of activating pro MMP-2, that MT-MMP-2 is different from MT-MMP-2, and that MT-MMP-3 is identical to MT-

MMP2 (see page 6, second paragraph), the specification does not disclose specifically what proteins are encompassed within the designations. Absent such disclosure, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

Claim 14 recites the "activation capability of pro MMP-2"; however, the specification fails to disclose the metes and bounds of such capability. The specification discloses MMP-2 as capable of activating pro MMP-2 (see page 6, lines 6-7); it does not disclose any activation capability that pro MMP-2 itself possesses. It is thus unclear if the claim is drawn to an activity which pro MMP-2 possesses or if it is drawn to the activity of MMP in activating pro MMP-2. Correction is required.

The claims are indefinite for referring to a protein "which has an activity identical with or substantially identical to naturally-occurring MT-MMP". The specification fails to disclose the metes and bounds of the claimed activity and fails to disclose the naturally occurring MT-MMP which is to be used for determining identical activity. Absent such disclosure, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

The term "substantially" is a relative term which renders the claims indefinite. The term "substantially"" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The claims are also indefinite for recitation of a "partial peptide", as the specification fails to teach the parameters of such a peptide. It is unclear how much of the complete peptide the partial peptide must include in order to be encompassed within the claimed invention.

The term "substantially" in claim 18 is also a relative term for the same reasons as those outlined *supra.*

Claim 15 recites a "protein which has an activity or a primary structural conformation identical with or substantially equivalent to that of MT-MMP-3 or a salt thereof". The claim is indefinite because

the specification fails to teach either the activity(ies) or the structural conformation which is to be used as the means of determining whether a protein is encompassed within the claimed invention. It is noted that a protein has a primary structure which is an amino acid sequence and a secondary structure involving folding and conformation. It is thus unclear what is encompassed within a "primary structural conformation".

Claim 20 is indefinite for recitation of an antibody which is "anti-serum". "Antiserum" is an art-recognized term for a preparation of serum obtained from an animal immunized so as to produce antibodies against a target antigen. It comprises a plurality of antibodies. It is thus unclear how a single antibody can be considered to be "anti-serum". Correction is required.

Claim 26 is indefinite because the claim recites "the method for detecting and/or measuring MT-MMP-3" and simultaneously recites "the detection and/or measurement of MT-MMP-3". It is unclear if the recitation which appears in parentheses is intended to encompass some undefined secondary method of if it is intended to reference the same method. Correction is required.

Claims 14-22 and 26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a "written description" rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the

invention. The invention, for purposes of the "written description" inquiry, is *whatever is now claimed*" (see page 1117).

A review of the language of the claim indicates that these claims are drawn to a genus, i.e., a genus of antibodies directed against matrix metalloproteinase proteins (MMP) which are capable of activating pro MMP-2 proteins and which have the same or a substantially equivalent activity of a naturally occurring membrane type MMP (MT-MMP). The claimed genus also encompasses antibodies against portions of the MMP.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention".

There is a single species of the claimed genus of proteins disclosed that is within the scope of the claimed genus, *i.e.* the MMP which consists of the sequence of SEQ ID NO:2. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claims encompass numerous species that are not further described. There is substantial variability among the species. There is no precise definition by

structure or formula or chemical name of any structural feature which is common to the members of the claimed genus.

One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus of which comprises antibodies directed against any and all proteins which are capable of activating pro MMP-2 and which have an activity in common with naturally occurring MT-MMP and antibodies directed against portions of those proteins. Furthermore, there is no written description of either a representative number of species or of a common structural feature of the genus which encompasses all naturally occurring MT-MMP. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (see *Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claims 14-22 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies directed against a MMP consisting of the amino acid sequence of SEQ ID NO:2 and for antibodies directed against membrane-associated MMP (MT-MMP), does not reasonably provide enablement for antibodies directed against any and all MMP which are capable of activating pro MMP-2 and which have any activity which is substantially equivalent to any naturally occurring MT-MMP. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification

must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to an antibody directed against a MMP which is capable of activating pro MMP-2 and which has an activity that is identical to or substantially equivalent to a naturally occurring MT-MMP, excluding MT-MMP-1. As was outlined *supra*, the claims are indefinite in that it is not clear what molecules are encompassed within the definitions of an MMP which is capable of activating pro MMP-2 and which molecules are excluded as equivalent to MT-MMP-1.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that the MMP associated with the cell surface (MT-MMP) have not yet been elucidated (see Young et al. Fibrinolysis 8/Suppl. 1:p56, 1994, second sentence of the abstract).

The amount of direction or guidance present and the presence or absence of working examples: Given the teachings of unpredictability found in the art regarding the identity and isolation of MMP, detailed teachings are required to be present in the disclosure in order to enable the skilled artisan to make and use antibodies directed against the broadly claimed group of MMP. Such teachings are absent. The specification discloses two MT-MMP, which are designated as MT-MMP-1 and MT-MMP-2 or MT-MMP-3 (see page 6, second paragraph). There is no disclosure of any other members of the claimed group of MT-MMP. There is no guidance as to how additional MT-MMP can by elucidated. The working examples are exclusively drawn to making a single species of MT-MMP, that designated as MT-MMP-2 or alternatively as MT-MMP-3.

The breadth of the claims and the quantity of experimentation needed: Given the teachings of unpredictability regarding isolation or elucidation of MT-MMP other that MT-MMP-1 or MT-MMP-2 which are found in the art and given the lack of teachings or guidance in applicant's disclosure regarding MT-MMP other than the two specifically referenced, it would require undue experimentation by one of skill in the art to make antibodies directed against MT-MMP and other undefined molecules having an activity substantially equivalent to that of a MT-MMP, commensurate in scope with the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14-22 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young et al. or in view of Serafini et al. (The Journal of Nuclear Medicine, 34/3:533-536).

The claimed invention is drawn to an antibody directed against a MMP which has an activity substantially equivalent to a naturally occurring MT-MMP and which is a pro MMP-2 activating factor, excluding MT-MMP 1. Dependent claims recite the MMP as having an amino acid sequence of SEQ ID NO:2 or a sequence which is substantially equivalent to the amino acid sequence of SEQ ID NO:2. Due to the phrase "an amino acid sequence represented by SEQ ID NO:2", the claims have been broadly interpreted as encompassing antibodies which are directed against proteins which encompass portions of the amino acid sequence of SEQ ID NO:2 (as little as a single amino acid can be reasonably considered to correspond to a portion of SEQ ID NO:2), as well as antibodies directed against proteins which encompass SEQ ID NO:2 in its entirety.

Young et al. teach MMP associated with the cell surface. Young et al. teach one such representative MMP as plasma membrane MMP-2. Young et al. teach that MMP are associated with cancer cells and that plasma membrane MMP-2 is associated with cancer cell invasiveness. Although Young et al. does not teach the amino acid sequence of plasma membrane MMP-2, absent some evidence to the contrary, the plasma membrane MMP-2 disclosed by Young et al. is equivalent to the MT-MMP of the claimed invention and inherently encompasses at least a portion of the amino acid sequence of SEQ ID NO:2.

Serafini teaches that monoclonal and polyclonal antibodies directed against specific antigens are routinely used in the art for diagnostic and therapeutic applications (see the entire document and especially page 533, the abstract and first four paragraphs).

One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have made a polyclonal or monoclonal antibody directed against the plasma membrane associated MMP-2 disclosed by Young et al. in order to make an antibody which could be used for diagnosis or therapy of cancer.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Official FAX telephone number is (703) 872-9306 and the After Final FAX telephone number is (703) 872-9307. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

Brenda Brumback
Patent Examiner